7:30-8:30 a.m.) using a scale in which symptoms were rated from 0 (=none) to 10 (=severe, persistent, annoying distraction) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:1-2]. No rescue medications were allowed during the study.

Reviewer's Note: Use, by the sponsor of the FLONASE efficacy supplement, of only 1 nasal symptom score for study entry criteria (the nasal stuffiness-nasal congestion score) is in contrast to the TNSS seen in other sponsor's submission(s) where a more global symptom score has generally been used for screening purposes. While not unacceptable, the drawback of using only 1 symptom score to determine eligibility of patients to enter the randomization phase of the study is the potential biasing of the study population enrolled, namely those patients with more severe nasal congestion. Patients with potentially severe allergic rhinitis due to rhinorrhea, sneezing, but perhaps less troublesome nasal congestion, would not be captured with this method.

On Day 1 of the park ('acute') phase of the study, patient symptoms were assessed hourly at 7:30 and 8:30 a.m., the 1st dose of study medication was given at 9:00 a.m., and then symptoms were assessed hourly until 4:00 p.m. (~ 7 hours total). Patients were asked to record symptoms on their diary cards that reflected their symptoms within the previous hour. After completion of the park day (4:00 p.m.), patients returned to their homes and symptoms were rated again at 6:00 p.m. and 9:00 p.m. (just prior to the next dose of study medication or 12 hours post-initiation of treatment).

On Day 2 of the park study, patients again returned to the outdoor setting and completed diary cards at 8:00 a.m. to reflect their morning symptoms within the previous hour. Study medication was taken at 9:00 a.m. and patients again remained in the park till 4:00 p.m. and recorded their SAR symptoms hourly in a similar manner as performed on Day 1 of the study. Likewise, patients recorded the 6:00 p.m. and 9:00 p.m. symptoms at home.

During the 'chronic' phase of the study (which will not be evaluated in this onset of action review in any great detail), symptoms continued to be assessed twice daily at 8:00 a.m. (prior to a.m. dosing) and at 9:00 p.m. (just prior to p.m. dosing).

The primary efficacy endpoint for this study was the onset of action in the park phase of the study. Onset of action was defined as the first time point at which a sustained (i.e. more than one time point), statistically significant difference in the total nasal symptom score was shown between FP treatment and placebo for the intent-to-treat population [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:3], compared to baseline TNSS. For this calculation, baseline was defined as the average of the 7:30 a.m. and 8:30 a.m. scores prior to treatment on the 1st day of treatment.

Onset of action was analyzed by ANOVA, with evaluation of change from baseline, controlling for investigator. Overall tests for treatment effects were

conducted and if the overall test was statistically significant ($p < 0.05$), pairwise comparisons between treatments were evaluated for between-treatment differences. If the overall p-value was not statistically significant, pairwise p-values were viewed as descriptive [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:3]. The study was powered such that 96 patients/treatment arm would provide at least 90% power to detect a 20% difference in mean improvement between placebo and FP treatment. In addition to hourly analysis of the onset of action, the hourly symptom data were group into two, 3-hour intervals: 11:00 a.m.-1:00 p.m., and 2:00 p.m.-4:00 p.m. The 10:00 a.m. assessment was not included in any period as there was no expectation that the onset of action could begin in < 1 hour. Analysis of onset of action by this latter arbitrary grouping of time points was avoided in the medical officer review, as a more specific time frame of onset of action was desired. Hence, change in TNSS was evaluated by the medical officer by evaluating the hourly change in TNSS for the 1st 7 hours post-initiation of treatment, along with the 6:00 p.m. (9 hours post-initiation of treatment), the 9:00 p.m. (12 hours post-initiation of treatment) time point, and the 8:00 a.m. (23 hours post-initiation of treatment) time point. A number of secondary efficacy endpoints were additionally analyzed in this study which will not be further elaborated upon in this onset of action review.

8.7.1.c. Results

Patient demographics and patient baseline rhinitis symptoms (including the TNSS) were similar at baseline and were comparable between the 3 treatment groups. The groups had mild to moderate baseline nasal symptoms, with a mean baseline TNSS symptom range (defined as the average of the 7:30 a.m. and 8:30 a.m. pre-treatment scores) of 26.5 to 27.3 (overall p-value=0.854 across treatment groups) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:4-5].

A total of 14 (5%) of patients withdrew from the study: 4 (4%) for the placebo group, 2 (2%) from the FP group, and 8 (8%) from the BDP group [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:4]. Missing symptom scoring was handled as described in the NAPR and PAR studies previously reviewed. Only minimal use of specifically excluded medications (e.g. antihistamines, corticosteroids) occurred during the trial, with most concomitant medication use consisted of acetaminophen, ibuprofen, aspirin, and estrogens/progestogens [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:4].

Using the change from baseline (pre-treatment with study medication) in patient hourly self-rated TNSS as the primary endpoint to determine onset of action, results of the 3 treatment groups are presented in Table I. Based on these data, the FP Nasal Spray treated patients demonstrated a sustained statistically significant decrease in TNSS when compared to placebo treatment **4 hours** post-initiation of treatment with FP Nasal Spray (p=0.001) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:17]. Of note, the onset of

action for BDP Nasal Spray in this study (FLN 444) was **3 hours** post-initiation of treatment. For both active treatments, a statistically significant decrease in TNSS compared with placebo treatment was sustained for the remainder of the 36 hour treatment interval (Day 1 and Day 2) where morning hourly assessments of rhinitis symptom severity were recorded. The range in change from baseline in the TNSS for the FP treatment group was from [redacted] points (on a maximum scale of 80), for the BDP treatment, this range was from [redacted] points, and for the placebo group, this range was from [redacted] points for this 36 hour period duration [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:17]. Importantly, this numerical range was not very different between either of the 3 treatment groups, including the FP Nasal Spray treatment group and the placebo group, even though statistical significance (a 20% difference in TNSS0 was reached between these 2 treatments.

Review of the individual nasal symptoms and their relative contribution in determining the overall TNSS was performed by the medical officer, in order to rule out disproportionate contribution of any one nasal symptom in determination of the TNSS. Based on the data provided for study FLN-444 by the sponsor, which were only available for the sum of left and right acute stuffy nose and the sum of left and right acute sniffles/runny nose, both of these symptoms numerically contributed approximately equally to determination of the TNSS [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:19-20], with a slightly greater contribution by the stuffy nose symptom score. Furthermore, a more consistent decrease in the acute stuffy nose symptom was seen, compared to acute sniffles/runny nose (all p-values except for 2, 1 hour post-dosing on Day 1 and 1 hour post-dosing on Day 2 of the study), suggestive that this symptom (stuffy nose or nasal congestion) may have been a more important contributor to the overall direction of TNSS decrease with FP Nasal Spray treatment than the runny nose (rhinorrhea) symptom.

Of note, for the 'chronic' portion of the study (Days 3-7 of the study, during which symptoms were recorded twice daily, ~ 12 hours apart), a statistically significantly greater decrease in patient self-rated TNSS was seen in the FP treated patients compared to placebo treated patients (p-value range for days 3-7 for the FP group compared to placebo: $p < 0.001$ to $p=0.018$) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:21]. Likewise, similar results were seen in the BDP treated patients (p-value range for days 3-7 for the BDP group compared to placebo: $p < 0.001$ to $p=0.019$) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:21].

In summary, based on this onset of action study, FP Nasal Spray (as also BDP Nasal Spray) demonstrated onset of action within 12 hours, compared to placebo treatment when statistically significant differences between active treatment and placebo were compared. Numerically however, the differences between FP Nasal Spray and placebo were small (2.8 to a 3.3 point difference between FP Nasal Spray and placebo on a 0-80 numerical scale).

Table I.

Onset of Action of Flonase Nasal Spray vs. Placebo vs. BDP Nasal Spray: Study FLN 444; Hourly Patient Self-Rated Total Nasal Symptom Scores Intent-to-Treat (ITT) for Day 1 and Day 2 of the Park Study
[NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:17]

	TREATMENT GROUPS					
	Placebo	[1]FP 200 µg qd	[2]BDP 168 µg bid	P vs. FP 200	P vs. BDP 168	FP 200 vs. BDP 168
Total Nasal Symptom Score (TNSS): **Sum of nasal stuffiness (right nostril), nasal stuffiness (left nostril), number of nose blows, number of sneezes, sniffles/runny nose (right nostril), sniffles/runny nose (left nostril), post-nasal drip, and nasal itching.**						
DAY 1						
Baseline =9:00 am (n, mean score)	102, 27.3	104, 26.5	103, 26.7	0.600	0.662	0.931
1 hour post-Rx (n, mean score, Δ)	102, 24.6, -2.7	104, 21.6, -5.0	103, 22.0, -4.6	0.035	0.075	0.747
2 hours " (n, mean score, Δ)	102, 21.5, -5.8	103, 19.0, -7.5	103, 18.6, -8.0	0.172	0.073	0.668
3 hours " (n, mean score, Δ)	102, 21.0, -6.3	104, 18.3, -8.3	103, 17.0, -9.6	0.126	0.009	0.268
4 hours " (n, mean score, Δ)	102, 22.5, -4.8	104, 17.3, -9.2	103, 17.0, -9.7	0.001	<.001	0.714
5 hours " (n, mean score, Δ)	102, 21.5, -5.8	104, 16.8, -9.8	103, 16.6, -10.1	0.005	0.002	0.820
6 hours " (n, mean score, Δ)	102, 21.7, -5.7	104, 17.7, -8.8	103, 16.6, -10.0	0.026	0.002	0.389
7 hours " (n, mean score, Δ)	102, 22.1, -5.2	104, 17.1, -9.5	103, 16.3, -10.4	0.003	<.001	0.493
9 hours " (n, mean score, Δ)	101, 23.4, -3.9	104, 17.8, -8.8	103, 19.1, -7.6	<.001	0.011	0.410
12 hours " (n, mean score, Δ)	100, 24.5, -3.0	104, 17.2, -9.3	103, 19.9, -6.8	<.001	0.014	0.104
23 hours " (n, mean score, Δ)	100, 25.3, -2.2	100, 21.0, -5.8	99, 20.2, -6.6	0.008	0.001	0.540
DAY 2						
0 hours (n, mean score, Δ)	100, 23.4, -4.0	102, 19.3, -7.3	99, 16.9, -9.9	0.015	<.001	0.053
1 hour post-Rx (n, mean score, Δ)	100, 21.4, -6.1	102, 17.6, -9.1	98, 15.7, -11.2	0.036	<.001	0.106
2 hours " (n, mean score, Δ)	100, 19.0, -8.4	102, 14.9, -11.8	97, 12.9, -14.3	0.024	<.001	0.102
3 hours " (n, mean score, Δ)	100, 18.1, -9.3	102, 14.0, -12.7	97, 12.3, -14.9	0.022	<.001	0.132
4 hours " (n, mean score, Δ)	100, 17.3, -10.2	102, 13.4, -13.3	97, 10.9, -16.3	0.040	<.001	0.051
5 hours " (n, mean score, Δ)	100, 16.9, -10.6	102, 12.3, -14.4	97, 11.2, -15.9	0.014	<.001	0.308
6 hours " (n, mean score, Δ)	100, 16.0, -11.4	102, 12.5, -14.1	97, 11.3, -15.8	0.080	0.005	0.278
7 hours " (n, mean score, Δ)	100, 16.0, -11.4	102, 12.0, -14.7	97, 11.4, -15.7	0.042	0.008	0.525
9 hours " (n, mean score, Δ)	100, 18.4, -9.0	102, 13.7, -13.0	97, 14.6, -12.5	0.013	0.028	0.784
12 hours " (n, mean score, Δ)	99, 19.7, -7.7	102, 14.0, -12.7	97, 15.5, -11.7	0.001	0.010	0.527

[1]FP=Fluticasone propionate. [2]BDP=Beclomethasone dipropionate.
NOTE: Standard Errors not included in this table. For standard errors refer to Table 6 in Vol 35.2 of the efficacy supplement. P-values are based on the ANOVA test on change from baseline, controlling for investigator. Baseline is defined as the average of the 7:30 a.m. and 8:30 a.m. scores prior to treatment on the 1st day of treatment.

8.7.2. Protocol No. FLN 445: A double-blind, placebo-controlled, randomized, parallel group park study to compare the onset of action of fluticasone propionate (FP) aqueous nasal spray 200 μg qd vs. beclomethasone dipropionate aqueous nasal spray (BDP) 168 μg bid in patients with seasonal allergic rhinitis (SAR).

Principal Investigator: None, multi-center study.

Participating Centers: 3 U.S. centers (Albany (NY), Greenville (NC), Aurora (CO)).

8.7.2.a. Objectives

As study FLN-444, the primary objective of this study was to investigate the onset of action of fluticasone propionate nasal spray vs. placebo and vs. an active comparator, BDP Nasal spray; though efficacy and safety for the duration of the 7 day period (days 3-7; the length of the trial) were also evaluated.

8.7.2.b. Study Design

The study design of FLN-445 was identical to that of study FLN-444 as these were replicate park studies to determine the onset of action of FP Nasal Spray [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:98-100]. Again, baseline symptom scores were defined in the same manner as in FLN-445, as was the primary efficacy endpoint to determine the onset of action: the 1st statistically significant sustained change from baseline in TNSS (=composite score comprised of the sum of the individual symptom scores of: nasal stuffiness (right nostril), nasal stuffiness (left nostril), number of nose blows, number of sneezes, sniffles/runny nose (right nostril), sniffles/runny nose (left nostril), post-nasal drip, and nasal itching) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:98-100].

8.7.1.c. Results

A total of 319 patients with SAR were randomized into study FLN-445: 106 in the placebo group, 106 in the FP group, and 107 in the BDP group [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:101]. Patient demographics and patient baseline rhinitis symptoms (including the TNSS) were similar at baseline and were comparable between the 3 treatment groups. The groups had mild to moderate baseline nasal symptoms, with a mean baseline TNSS symptom range (defined as the average of the 7:30 a.m. and 8:30 a.m. pre-treatment scores) of 25.8 to 26.3 (overall p-value=0.951 across treatment groups) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:102].

A total of 15 (5%) of patients withdrew from the study: 4 (4%) from the placebo group, 8 (8%) from the FP group, and 3 (3%) from the BDP group [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:101].

Failure to return to the study was cited as the most common reason for patient withdrawal for all 3 treatment groups. Missing symptom scoring was handled as described in the NAPR and PAR studies previously reviewed. Only minimal use of specifically excluded medications (e.g. antihistamines, corticosteroids) occurred during the trial, with most concomitant medication use consisting of acetaminophen, ibuprofen, and aspirin [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:101].

Using the change from baseline (pre-treatment with study medication) in patient hourly self-rated TNSS as the primary endpoint to determine onset of action (same clinical endpoint as for study FLN-444), results of the 3 treatment groups are presented in Table II. Unlike study FLN-444 however, the FP Nasal Spray treated patients did not demonstrate a sustained statistically significant decrease in TNSS when compared to placebo treatment **at any time point during the study with the exception of an 11 hour period (from 12 hours-23 hours post-treatment)** post-initiation of treatment with FP Nasal Spray (p=0.029 at 12 hours and p=0.041 at 23 hours for FP vs. placebo) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:103]. Of note, the onset of action for BDP Nasal Spray in this study (FLN 444) was **23 hours** post-initiation of treatment which was not sustained for the entire hour and was sustained from 2-4 hours post-treatment with BDP Nasal Spray on Day 2 of the acute phase of the study, as compared with placebo treatment. Hence, for this study, FP Nasal Spray demonstrated a somewhat 'faster' onset of action than did BDP Nasal Spray, in contrast to study FLN-444. The range of the change from baseline in the TNSS for the FP treatment group was from [redacted] points (on a maximum scale of 80), for the BDP treatment group. This range was from [redacted] to [redacted] points (note: very similar range to the FP treatment group), and for the placebo group, this range was from [redacted] points for this 36 hour period duration [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:115]. These numerical differences were similar to those shown in FLN-444, and overall were deemed to be small differences for the active treatments (FP and BDP) by the reviewing medical officer.

Reviewer's Note: Interestingly, in this study placebo group patients demonstrated a significant decrease in TNSS, which was greater than that observed in study FLN-445. The etiology of this discrepancy is unknown but could possibly be due to a significant placebo effect or inadvertant administration of an active drug treatment (either FP or BDP) than placebo treatment. Hence, the possibility of a significant placebo response seen in this study could be responsible for lack of a consistent statistically significant difference in decreasing TNSS between FP treatment and placebo. The sponsor was not able to offer an explanation of this effect, however they believed to be a true placebo effect, as being secondary to a flushing action of the spray which may be effective in clearing secretions from the nose [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.1:30]. In addition, the sponsor noted unseasonable weather at 2 of the 3 investigational

sites during performance of the acute phase of the park study for FLN -445 which affected the pollen counts (though no pollen counts were provided by the sponsor in this addendum to the efficacy supplement) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.1:33].

Review of the individual nasal symptoms and their relative contribution in determining the overall TNSS was again performed by the medical officer, in order to rule out disproportionate contribution of any one nasal symptom in determination of the TNSS. Based on the data provided for study FLN-445 by the sponsor, which were again only available for the sum of left and right acute stuffy nose symptom score and the sum of left and right acute sniffles/runny nose symptom score, both of these symptoms numerically contributed approximately equally to determination of the TNSS [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:117-118], with again, a slightly greater contribution by the stuffy nose symptom [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:117]. In study FLN-445, Furthermore, for both the acute stuffy nose symptom and sniffles/runny nose symptom, most time points failed to demonstrate a statistically significant difference between FP Nasal Spray and placebo treatment with the exception of 1 time point (t=3 hours post-treatment on Day 2 for acute stuffy nose) and 5 time points for the sniffles/runny nose symptom (t=Day 1, 2 hours post-treatment, t=Day 1, 12 hours post-treatment, Day 2, 2 hours post-treatment, Day 2, 4 hours post-treatment, and t=Day 2, 12 hours post-treatment) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:117-118]. Based on these results, it is difficult to conclude if either nasal symptom was more important in determining the statistical trend for this study, but it appears that overall both contributed approximately equally.

Of note, for the chronic portion of the study (Days 3-7 of the study, during which symptoms were recorded twice daily, ~ 12 hours apart), a statistically significantly greater decrease in patient self-rated TNSS was not consistently seen in the FP treated patients compared to placebo treated patients (p-value range for days 3-7 for the FP group compared to placebo: p=0.004 to p=0.126) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:119]. Likewise, similar results were seen in the BDP treated patients in which consistent statistically significant differences between BDP treatment and placebo were not demonstrated at every time point (p-value range for days 3-7 for the BDP group compared to placebo: p< 0.001 to p=0.109) [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:119].

In summary, based on this onset of action study FLN-445, FP Nasal Spray demonstrated onset of action from 12 hours-23 hours (the end-of dosing interval of the 1st dose) post-initiation of therapy with FP Nasal Spray, compared to placebo treatment. A very strong trend in decreasing TNSS was noted at 9 hours, with statistical significance for the FP treatment group seen at 12 hours and at the end-of-dosing interval, compared to placebo. Likewise, and similar to study

FLN-444, the numerical differences in the change in TNSS for the FP treatment group compared to placebo were small, albeit statistically significant.

Table II.

Onset of Action of Flonase Nasal Spray vs. Placebo vs. BDP Nasal Spray: Study FLN 445; Hourly Patient Self-Rated Total Nasal Symptom Scores Intent-to-Treat (ITT) for Day 1 and Day 2 of the Park Study

[NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.2:115]

	TREATMENT GROUPS					
	Placebo	[1]FP 200 µg qd	[2]BDP 168 µg bid	P vs. FP 200	P vs. BDP 168	FP 200 vs. BDP 168
Total Nasal Symptom Score (TNSS): Sum of nasal stuffiness (right nostril), nasal stuffiness (left nostril), number of nose blows, number of sneezes, sniffles/runny nose (right nostril), sniffles/runny nose (left nostril), post-nasal drip, and nasal itching.						
DAY 1						
Baseline =9:00 am (n, mean score)	105, 26.2	105, 26.3				
1 hour post-Rx (n, mean score, Δ)	104, 21.4, -4.8	105, 21.2, -5.1	106, 20.8, -5.0	0.784	0.832	0.950
2 hours " (n, mean score, Δ)	104, 18.8, -7.4	105, 17.8, -8.5	106, 18.8, -7.0	0.402	0.759	0.251
3 hours " (n, mean score, Δ)	104, 17.2, -9.1	105, 16.2, -10.1	106, 16.9, -8.9	0.399	0.867	0.310
4 hours " (n, mean score, Δ)	104, 16.5, -9.7	104, 15.4, -11.0	106, 16.5, -9.2	0.291	0.717	0.155
5 hours " (n, mean score, Δ)	104, 15.9, -10.4	104, 15.2, -11.2	106, 15.9, -9.9	0.524	0.758	0.343
6 hours " (n, mean score, Δ)	104, 15.0, -11.3	104, 14.6, -11.8	106, 14.8, -11.0	0.712	0.848	0.573
7 hours " (n, mean score, Δ)	103, 15.0, -11.4	104, 14.9, -11.5	106, 14.6, -11.1	0.953	0.844	0.797
9 hours " (n, mean score, Δ)	103, 17.9, -8.6	104, 15.0, -11.4	106, 16.4, -9.4	0.056	0.559	0.179
12 hours " (n, mean score, Δ)	103, 20.4, -6.0	104, 17.0, -9.4	106, 17.6, -8.2	0.029	0.150	0.449
23 hours " (n, mean score, Δ)	102, 23.0, -3.3	99, 20.3, -6.0	104, 19.7, -6.0	0.041	0.044	0.955
DAY 2						
0 hours (n, mean score, Δ)	102, 20.1, -6.3	98, 18.9, -7.3	104, 17.5, -8.2	0.369	0.127	0.543
1 hours post-Rx (n, mean score, Δ)	102, 18.2, -8.2	98, 16.5, -9.7	104, 15.5, -10.2	0.254	0.141	0.756
2 hours " (n, mean score, Δ)	102, 17.7, -8.7	98, 14.7, -11.6	104, 13.9, -11.8	0.048	0.030	0.867
3 hours " (n, mean score, Δ)	102, 16.5, -9.9	98, 14.1, -12.2	104, 12.7, -13.0	0.135	0.039	0.587
4 hours " (n, mean score, Δ)	102, 15.7, -10.7	98, 12.7, -13.5	104, 11.8, -13.9	0.060	0.029	0.783
5 hours " (n, mean score, Δ)	102, 13.3, -13.1	98, 12.1, -14.1	104, 11.0, -14.7	0.442	0.260	0.731
6 hours " (n, mean score, Δ)	102, 13.4, -12.9	98, 11.7, -14.5	104, 11.0, -14.7	0.252	0.213	0.936
7 hours " (n, mean score, Δ)	102, 13.3, -13.1	98, 11.3, -14.9	104, 10.9, -14.8	0.220	0.260	0.907
9 hours " (n, mean score, Δ)	102, 14.9, -11.5	98, 12.5, -13.7	104, 13.1, -12.6	0.111	0.411	0.430
12 hours " (n, mean score, Δ)	102 16.3, -10.1	98, 13.4, -12.8	104, 14.2, -11.5	0.060	0.314	0.367

[1]FP=Fluticasone propionate. [2]BDP=Beclomethasone dipropionate.

NOTE: Standard Errors not included in this table. For standard errors refer to Table 6 in Vol 35.2 of the efficacy supplement. P-values are based on the ANOVA test on change from baseline, controlling for investigator. Baseline is defined as the average of the 7:30 a.m. and 8:30 a.m. scores prior to treatment on the 1st day of treatment.

Table IV.

Summary Table of Well-Designed Pivotal Studies in NDA 20-121 which evaluated Onset of Action; Intent-to-Treat (ITT) Population

[NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.1:36]

	Mean Change from Baseline in [1]TNSS											
Study Number	DAY 1 (=12 hours)			DAY 2			DAY 3			DAY 4		
	[2]PBO	[3]FP	[4]P-value	PBO	FP	P-value	PBO	FP	P-value	PBO	FP	P-value
SAR STUDY (ADULT): TNSS range from 0-400 points												
***FLN-203**	-21.8	-58.9	0.006	-24.5	-81.5	< 0.001	-28.8	-94.8	< 0.001	-33.4	-113.6	< 0.001

[1]TNNS comprised a sum of patient rated rhinorrhea, nasal obstruction, nasal itching and sneezing for all SAR (including pediatrics), PAR, and NAPR studies. For the 2 'onset of action studies' FLN-444 and FLN-445, TNSS was defined as: the sum of nasal stuffiness (right nostril), nasal stuffiness (left nostril), number of nose blows, number of sneezes, sniffles/runny nose (right nostril), sniffles/runny nose (left nostril), post-nasal drip, and nasal itching.

[2]PBO=Placebo [3]FP=Fluticasone propionate. [4]P-values are based on changes from baseline and were only depicted for statistically significant p-values, defined as a $p \leq 0.05$. No adjustments were made for multiple comparisons.

P-values in this table represent those for the FP 200 μg qd dose.

NOTE: Studies marked with an asterisk (*) and bolded represent studies which were considered pivotal studies in NDA 20-121.

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8.7.3. Summary of Onset of Action Data for SAR, PAR, and NAPR Studies Where This Endpoint Was Evaluated.

Results of a number of additional studies were submitted by the sponsor (summarized in Appendix I and in Table III) in which onset of action was assessed via twice daily patient self-rated TNSS scoring on diary cards for at least the first day of the study, and for some studies, if not twice daily then once daily thereafter. A total of 20 studies were submitted by the sponsor, in addition to the 'onset of action' studies FLN-444 and FLN-445, to support the sponsor's onset of action claim, however importantly, not all of these studies were utilized in the original review of NDA 20-121 (for the SAR and PAR indication for FLONASE), e.g. studies FLN-411, FLN-412, FLTA4004, FLTA4006, and FLTA4024. Nonetheless, all of these studies were double-blind, placebo-controlled, parallel group studies in which patients entered a screening period during which eligibility for the study was determined and baseline severity of nasal symptoms was established. Efficacy data from all patients who qualified for enrollment and were exposed to study drug during the 1st 4 days of double-blind treatment was analyzed by performing hypothesis tests on patient self-rated TNSS for the ITT population. The dosing regimen evaluated in these 20 studies consisted of FP Nasal Spray 200 µg qd for adults for the SAR and PAR indication, FP Nasal Spray 200 µg bid for the adult NAPR indication, and FP Nasal Spray 100 µg qd for the pediatric SAR indication [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.1:30]. A brief summary of these studies (including study duration, study medication doses and the number of patients randomized into each treatment group) is provided in Appendix I of this section.

Based on review of all 20 studies, onset of action within 12 hours post-dosing with the 1st dose was demonstrated in 4 out of the 20 studies submitted by the sponsor to this efficacy supplement (FLN-203, FLN-230, FLN-402, and FLN-320). Of those studies that did not demonstrate onset of action after 12 hours of treatment with FP Nasal Spray, trends toward statistical significance at the 12 hour time point were not seen in most of these studies (exception, studies FLN—305 and FLN-411). The majority of these studies (14 out of 20) did however show onset of action by 24 hours, although again, of those that did not, a trend toward statistical significance was not generally seen.

Reviewer's Note: Importantly, several confounding issues were noted on review of these studies and by the sponsor's own admission, particularly in those studies which failed to demonstrate onset of action for the FP treatment group 12 hours after initiation of treatment. Rescue medication use (the antihistamine chlorpheniramine maleate) was allowed in a number of studies (FLN-203, FLN-204, FLN-301, FLN-305, FLN-306, FLN-310, FLN-311, FLN-320, and FLN-321) for the treatment of intolerable symptoms during the double-blind treatment period and use of rescue medication was generally found to be higher in the placebo group patients in these 9 studies [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.1:31, 115-121]. All of these studies, with the

exception of study FLN-203 (one of the pivotal studies for NDA 20-121), failed to demonstrate a statistically significant sustained decrease in TNSS when FP Nasal Spray treatment was compared to placebo treatment at the 12 hour time point.

An additional complicating feature in the analysis of these 20 studies may have also included different a priori specifications for powering of the study and definition of what change in TNSS would constitute a clinically significant difference in TNSS between FP treatment and placebo. For at least one study (FLN-270), rather than the 20% difference in TNSS pre-specified for the 2 'onset of action' park studies (FLN-444 and FLN-445), the required difference to attain statistical significance was a 30% difference in TNSS, a relatively large symptom score difference which, based on experience with rhinitis trials, may have made onset of action (per the accepted definition), difficult to demonstrate in this study because of this a priori efficacy requirement [NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.3:3, 115-121].

Thus, because of the inherent flaws in many of the representative onset of action studies provided by the sponsor in this submission, a re-analysis of only those pivotal studies for NDA 20-121 in which no known confounding issues were noted were examined by the medical officer. Excluding pivotal studies in which rescue medication use was allowed (even during the start of the trial), only 1 pivotal study was deemed to represent a well conducted clinical trial—SAR study FLN-203. Study FLN-203 showed an onset of action 12 hours post-initiation of study medication, which again would suggest that in a clean trial where placebo response (from any of a number of reasons—rescue medication use, 'true' placebo effect, etc.) was a not dominating feature, an onset of action in a majority of patients could be expected within 12 hours of treatment with FP Nasal Spray. A summary table of this 1 trial, with the mean change in TNSS from baseline and p-value for the FP 200 μg qd dose, when compared with placebo is provided in Table IV.

8.7.4.1. CONCLUSION

Based on review of the 2 'onset of action' park studies and review of the less confounded pivotal rhinitis trial from NDA 20-121 (Study FLN-203) which evaluated a 12 hour time point post-initiation of treatment with FP Nasal Spray, a 12 hour onset of action of FP Nasal Spray, as defined by a sustained statistically significant reduction in TNSS compared to placebo treatment, was demonstrable.

Table III.
Summary Table of Onset of Action for All Studies in Which this TNSS was Reviewed at 12 hours post-initiation of treatment; Intent-to-Treat (ITT) Population
[NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.1:36, 35.2:17, 21, 48-115]

	Mean Change from Baseline in [1]TNSS											
Study Number	DAY 1 (=12 hours)			DAY 2			DAY 3			DAY 4		
	[2]PBO	[3]FP	[4]P-value	PBO	FP	P-value	PBO	FP	P-value	PBO	FP	P-value
ONSET OF ACTION STUDIES: TNSS range from 0-80 points												
FLN-444	-3.0	-9.3	<0.001	-7.7	-12.7	0.001	-7.5	-11.2	0.018	-6.5	-11.2	0.004
FLN-445	-6.0	-9.4	0.029	-10.1	-12.8	0.060	-7.8	-10.3	0.126	-8.6	-11.5	0.084
SAR STUDIES (ADULT): TNSS range from 0-400 points												
*FLN-203	-21.8	-58.9	0.006	-24.5	-81.5	<0.001	-28.8	-94.8	<0.001	-33.4	-113.6	<0.001
*FLN-204	-14.6	-35.5	0.272	-35.5	-71.6	0.011	-47.4	-101.3	<0.001	-43.1	-99.8	<0.001
FLN-230	-24.7	-67.2	<0.001	-14.8	-91.2	<0.001	-33.2	-109.6	<0.001	-32.9	-118.6	<0.001
FLN-270	-29.3	-25.0	0.459	-37.9	-43.2	0.355	-44.0	-61.7	0.096	-53.7	-81.8	0.008
*FLN-301	-12.9	-26.6	0.246	-30.4	-67.4	0.012	-45.0	-93.9	<0.001	-48.4	-104.8	<0.001
*FLN-305	-22.3	-47.1	0.057	-45.3	-74.6	0.030	-57.9	-91.0	0.027	-66.4	-95.2	0.061
*FLN-306	-13.0	-39.7	0.166	-25.6	-73.5	0.008	-40.6	-92.5	0.003	-41.6	-107.1	<0.001
FLN-401	-35.2	-47.2	0.370	-48.8	-82.7	0.03	-60.3	-103.8	0.006	-63.1	-123.9	<0.001
FLN-402	-29.6	-45.1	0.032	-38.4	-66.4	<0.001	-53.4	-86.4	<0.001	-61.6	-99.1	<0.001
FLN-411	-41.6	-58.5	0.065	-52.6	-91.6	0.001	-73.3	-108.0	0.009	-66.9	-110.0	<0.001
FLN-412	-40.2	-50.2	0.463	-55.6	-69.1	0.262	-70.6	-95.2	0.051	-73.8	-106.8	0.013
FLTA4004	-44.9	-50.1	0.645	-60.4	-71.7	0.366	-71.3	-91.3	0.115	-84.6	-109.0	0.067
FLTA4006	-43.6	-54.8	0.244	-51.6	-80.3	0.009	-58.0	-99.7	<0.001	-58.2	-111.0	<0.001
FLTA4024	-45.4	-54.1	0.379	-59.7	-82.8	0.026	-74.9	-100.0	0.017	-70.7	-118.0	<0.001
SAR STUDIES (PEDIATRIC): TNSS range from 0-400 points												
FLN-320	-16.6	-39.4	0.136	-40.2	-58.9	0.079	-42.3	-70.6	0.134	-41.4	-71.4	0.01
FLN-321	-25.4	-38.3	0.638	-39.2	-62.5	0.132	-53.0	-70.5	0.554	-50.5	-78.9	0.026
PAR STUDIES (ADULT): TNSS range from 0-400 points												
*FLN-310	-3.0	-18.9	0.041	-9.4	-28.6	0.010	-12.8	-38.1	0.001	-7.3	-40.5	0.001
*FLN-311	-7.7	-15.8	0.230	-9.2	-25.1	0.023	0	-30.2	<0.001	-7.4	-28.8	0.006
NAPR STUDIES (ADULT): TNSS range from 0-300 points												
FLN-351	-19.9	-35.0	0.038	-29.5	-46.9	0.033	-36.4	-43.6	0.377	-38.8	-52.0	0.115
FLTA3010	-25.0	-27.6	0.663	-35.0	-38.2	0.550	-42.3	-46.6	0.459	-45.6	-56.4	0.095

[1]TNNS comprised a sum of patient rated rhinorrhea, nasal obstruction, nasal itching and sneezing for all SAR (including pediatrics), PAR, and NAPR studies. For the 2 'onset of action studies' FLN-444 and FLN-445, TNSS was defined as: the sum of nasal stuffiness (right nostril), nasal stuffiness (left nostril), number of nose blows, number of sneezes, sniffles/runny nose (right nostril), sniffles/runny nose (left nostril), post-nasal drip, and nasal itching.
[2]PBO=Placebo [3]FP=Fluticasone propionate. [4]P-values are based on changes from baseline and were only depicted for statistically significant p-values, defined as a $p \leq 0.05$. No adjustments were made for multiple comparisons.
The doses of FP Nasal Spray were either FP 200 µg qd or 200 µg bid for adult patients or FP 100 µg qd for pediatric patients though p-values in this table represent those for the FP 200 µg qd dose.
NOTE: Studies marked with an asterisk (*) and bolded represent studies which were considered pivotal studies in NDA 20-121.

Table IV.
Summary Table of Well-Designed Pivotal Studies in NDA 20-121 which evaluated Onset of Action; Intent-to-Treat (ITT) Population
[NDA 20-121, S-009, Supplement to the Efficacy Supplement, 01/30/98 35.1:36]

	Mean Change from Baseline in [1]TNSS											
Study Number	DAY 1 (=12 hours)			DAY 2			DAY 3			DAY 4		
	[2]PBO	[3]FP	[4]p-value	PBO	FP	P-value	PBO	FP	P-value	PBO	FP	P-value
SAR STUDY (ADULT): TNSS range from 0-400 points												
***FLN-203**	-21.8	-58.9	0.006	-24.5	-81.5	< 0.001	-28.8	-94.8	< 0.001	-33.4	-113.6	< 0.001

[1]TNNS comprised a sum of patient rated rhinorrhea, nasal obstruction, nasal itching and sneezing for all SAR (including pediatrics), PAR, and NAPR studies. For the 2 'onset of action studies' FLN-444 and FLN-445, TNSS was defined as: the sum of nasal stuffiness (right nostril), nasal stuffiness (left nostril), number of nose blows, number of sneezes, sniffles/runny nose (right nostril), sniffles/runny nose (left nostril), post-nasal drip, and nasal itching.
[2]PBO=Placebo [3]FP=Fluticasone propionate. [4]P-values are based on changes from baseline and were only depicted for statistically significant p-values, defined as a $p \leq 0.05$. No adjustments were made for multiple comparisons.
P-values in this table represent those for the FP 200 µg qd dose.
NOTE: Studies marked with an asterisk (*) and bolded represent studies which were considered pivotal studies in NDA 20-121.

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9.0. Integrated Summary of Efficacy

Three U.S. placebo-controlled studies were conducted with FP Aqueous Nasal Spray for the NAPR indication in adults and adolescents: study FLN 350, FLN 351, and FLTA 3010. All 3 studies were considered pivotal studies and included dosing regimens of FP 100 µg bid and FP 200 µg bid, along with placebo treatment. One study, FLTA 3010, was designed as a dose response study in which 3 doses of FP Nasal Spray were evaluated for efficacy (50 µg bid, of FP 100 µg bid and FP 200 µg bid). Importantly, for the NAPR indication, a 200 µg qd regimen was not studied in any of the 3 NAPR studies and a link between the FP 100 µg bid regimen in the NAPR studies was established to the FP 100 µg bid regimen to the FP 200 µg qd regimen in the PAR studies of NDA 20-121 (studies FLN 310 and FLN 311) which were shown to be comparable with regard to efficacy and the end-of-dosing interval. This comparability is used to substantiate approval for either a 100 µg bid dose of FP Nasal Spray or FP 200 µg qd in adults and children over the age of 4 years (extension of approval to children was based on use of the pediatric rule and prior approval of FP Nasal Spray for the SAR and PAR indication in children 4-11 years of age).

A summary of clinical trials reviewed in the NAPR efficacy supplement to NDA 20-121 is provided in Table I below.

Table I. Summary of Clinical Trials Reviewed in the NAPR Efficacy Supplement to NDA 20-121: FLONASE Aqueous Nasal Spray

STUDY	TREATMENT DURATION	TREATMENT ARMS:
Pivotal NAPR		
FLTA 3010	4 weeks	FP 50 µg bid, FP 100 µg bid, FP 200 µg bid, Placebo
FLN 350	4 weeks	FP 100 µg bid, FP 200 µg bid, Placebo
FLN 351	4 weeks	FP 100 µg bid, FP 200 µg bid, Placebo
Bridging PAR		
FLN 310	6 months	FP 100 µg bid, FP 200 µg qd, Placebo
FLN 311	6 months	FP 100 µg bid, FP 200 µg qd, BDP 168 µg bid, Placebo
Controlled, Non-U.S. Perennial Rhinitis (PAR and/or NAPR) Trials		
FLIP07	4 weeks	FP 50 µg bid, FP 100 µg bid, FP 200 µg bid, FP 400 µg bid
FLNT43	12 weeks	FP 200 µg qd, FP 200 µg bid, BDP 200 µg bid, Placebo
FLIT11	1 year	FP 200 µg bid, BDP 200 µg bid
FLIT22	1 year	FP 100 µg bid, Placebo
FLNP57	6 week	FP 200 µg qd, Placebo
FLNP64	4 weeks, followed by a 2 week washout period, followed by another 4 week treatment period (crossover)	FP 200 µg qd, Placebo
FLIT08	1 year (open label)	FP 200 µg bid
Pediatric, Non-U.S. Perennial Rhinitis (PAR and NAPR) Trials		
FLNT60	4 weeks	FP 100 µg qd, FP 200 µg qd, Placebo
FLNT61	12 weeks	FP 100 µg qd, FP 100 µg bid, FP 200 µg bid

While the marketed product strength for FLONASE Aqueous Nasal Spray is 50 μg/actuation; clinical trial formulations strengths were 12.5 μg/actuation, 25 μg/actuation, and 50 μg/actuation [NDA 20-121, S-009, 37:11]. The controlled trials for NAPR were conducted in 1191 patients ≥ 12 years of age for a duration of 28 days (4 weeks) of double-blind treatment. Study FLTA 3010 also evaluated 289 patients with NAPR treated with FP 200 μg bid for an additional 6 months (open-label extension). Studies FLN 351 and FLTA 3010 were fully recruited trials in which the target patient enrollment was attained, whereas FLN 350 was a single-center study for which target enrollment was not achieved. Study design summaries and patient enrollment for each of the 3 NAPR studies is summarized on page 12 of Vol. 37 of the sponsor's submission [NDA 20-121, S-009, 37:12] and patient exposure to study medication is summarized in Table II. below.

Table II. Patient Exposure to FLONASE Nasal Spray
All NAPR Studies: FLN 350, FLN 351, and FLTA 3010
[NDA 20-121, S-009, 38:65-66]

Treatment Group	# of Pts Exposed	Days 1-14	Days 15-28	Days 29-42	Days 43-61	Days 62-122	Days 123-183	Days 184-212	Days 213-237
Placebo	326	8	173	145	0	0	0	0	0
FP 50 μg bid	208	16	141	51	0	0	0	0	0
FP 100 μg bid	332	12	176	143	1	0	0	0	0
FP 200 μg bid	538	14	128	128	12	23	109	105	19

Other important study design considerations when evaluating efficacy for the 3 NAPR studies and the 2 PAR studies that were used to provide the comparability link between the FP 100 μg bid dose and the FP 200 μg qd dose was the prohibition of use of rescue medications for treatment of intolerable rhinitis symptoms during the double-blind treatment periods in all 3 NAPR studies. During the open-label period of FLTA 3010, rescue medications were allowed for intolerable rhinitis symptoms, with the exception of other intranasal steroids. Another important study design issue when evaluating efficacy was the discrepancy between the NAPR and PAR studies with regard the rhinitis symptoms used for the determination of the TNSS. Whereas the TNSS for the NAPR studies was comprised of the sum of: nasal obstruction, rhinorrhea, and **postnasal drip**; the TNSS for the PAR studies was comprised of the sum of: nasal obstruction, rhinorrhea, **sneezing**, and **nasal itching**. Because of these inherent differences in the definition of TNSS, the maximum TNSS score was likewise different between the NAPR and PAR studies; with a maximum TNSS score of 300 for the NAPR studies and a maximum TNSS score of 400 for the PAR.

9.1. Patient Demographics for the NAPR Studies

A total of 1191 patients were enrolled in the NAPR trials, of whom 289 participated in the open label safety extension of study FLTA 30130. Demographic data from the double-blind treatment period of the 3 NAPR studies are presented in Table III. below.

Table III. Patient Demographics in the 3 NAPR Studies
[NDA 20-121, S-009, 38:14, 70]

	Double-blind Treatment Period					Open-Label Period
-	Placebo (n-326)	FP 50 µg bid (n=208)	FP 100 µg bid (n=332)	FP 200 µg bid (n=325)	Total (n=1191)	FP 200 µg bid (n=289)
Gender: overall p-value=0.275						
Female	201	142	203	213	759 (64%)	189 (65%)
Male	125	66	129	112	432 (36%)	100 (35%)
Age (years): overall p-value=0.155						
Mean	43.1	42.7	41.8	40.6	42.1	43.3
Range	12-79	14-86	12-83	12-75	12-86	14-79
Ethnic Origin: overall p-value=0.541						
Caucasian	313	195	310	308	1126 (95%)	280 (97%)
Black	4	4	12	10	30 (3%)	1 (<1%)
Hispanic	8	8	9	4	29 (2%)	7 (2%)
Other	1	1	1	3	6 (<1%)	1 (<1%)
Duration of NAPR (years): overall p-value=0.581						
1-4 years	84	48	77	85	294 (25%)	63 (22%)
5-9 years	65	44	91	70	270 (23%)	77 (27%)
10-14 years	63	38	57	63	221 (19%)	52 (18%)
≥ 15 years	114	78	107	107	406 (34%)	97 (34%)

Based on the patient demographic characteristics delineated in Table I for all 3 NAPR studies, no significant differences were noted between the 4 different treatment groups (3 different FLONASE doses and placebo). Approximately 2/3 of patients in all 4 treatment groups were female, and the majority of all patients (male and female) were Caucasian, with a mean age of 42.1 years, and ≥ a 15 year history of NAPR. The patient demographics of the double-blind treatment period and open-label period were similar, as shown in Table II. above.

9.2. Summary of the Primary Efficacy Data for the NAPR Studies

Evaluation of the primary efficacy data for the 3 NAPR studies, all 3 of which were considered pivotal trials by the medical reviewer, consisted of an evaluation of the patient self-rated mean reflective daily TNSS comprised of the sum of rhinorrhea, nasal obstruction, and postnasal drip for each week of the double-blind period. A summary of the results for the 3 NAPR studies evaluated in this efficacy supplement for a fluticasone dose of 100 µg bid—the proposed 'to-be-marketed' dose, is provided in Table IV. below.

These data support efficacy for all 4 weeks of the double-blind period for NAPR study FLTA 3010, but only for weeks 1-3 for study FLN 350, and for no time points in study FLN 351. Importantly, both studies FLTA 3010 and FLN 351 (the 'failed' study) had adequate power to determine the primary efficacy endpoint, whereas as study FLN 350 had inadequate patient enrollment. Because of the smaller number of patients randomized into study FLN 350, the standard errors were also somewhat higher for FLN 350. The mean baseline TNSS in patients enrolled into the FP 100 μg bid group (along with the baseline TNSS for the placebo and other FP groups) was comparable for FLTA 3010 and FLN 350 but slightly lower in FLN 351. The mean change in weekly TNSS for these 3 studies (the 'effect size') were comparable for studies FLTA 3010 and FLN 350 (the 'failed' study), but somewhat lower for FLN 351. The greatest decrement in symptom scores was seen at weeks 3 and 4 post-initiation of treatment, and while not presented in Table III. below, discontinuation of treatment at week 4 with follow-up 1 week later revealed worsening of TNSS for the FP treatment arms (and also placebo, but greater for the FP groups) for all 3 NAPR studies. Hence, numerically, symptom score data in these 3 NAPR studies, as assessed by the primary efficacy variable, indicate that a reasonable decrement in TNSS occurred in all 3 NAPR studies, including 'failed' study FLN 350.

Review of the individual rhinitis symptom components showed that FLONASE (at all doses tested) demonstrated greatest efficacy in decreasing the NAPR symptom of nasal obstruction over that of rhinorrhea, postnasal drip, or sneezing.

Analysis of the duration of effect or end-of-dosing interval for the 3 NAPR studies was not readily evaluabe as reflective and no 'instantaneous' nasal symptom scores were quantified by patients. Nonetheless, information provided by the patient diary scores indicate that no significant differences were seen between a.m. and p.m. symptom scores (total and individual NAPR scores) throughout the double-blind treatment period for the 3 NAPR studies. Thus, at least for bid dosing, FP Nasal Spray appeared to show adequate efficacy in decreasing nasal symptoms when used twice a day and effects did not appear to wane significantly over the 12 hour period. Subgroup analysis of efficacy by age, gender, and ethnic origin was not performed in the 3 NAPR studies submitted to this efficacy supplement.

Table IV. Summary of Primary Efficacy Data for the FP 100 µg bid dose in the 3 NAPR Studies: FLTA 3010, FLN 350, and FLN 351

	TREATMENT GROUPS			P-value:		
	FLTA 3010: FP 100 µg bid	FLN 350: FP 100 µg bid	FLN 351: FP 100 µg bid	FLTA 3010: FP 100 µg bid c/w placebo	FLN 350: FP 100 µg bid c/w placebo	FLN 351: FP 100 µg bid c/w placebo
Total # Pts. at Screening	211	23	98			
Total Nasal Symptom Score (TNSS): Composite of Rhinorrhea + Nasal Obstruction + Postnasal Drip						
Pre-Treatment (day -6 to 0) (n, mean score ± [2]SE)	208 207.6 ± 3.0	23 204.6 ± 8.5	98 181.7 ± 3.9	0.321	0.938	0.935
Week 1 (day 1- 7) (n, Δ in score ± SE)	204 -54.9 ± 4.0	23 -56.3 ± 12.9	98 -35.1 ± 5.2	<0.001	0.034	0.561
Week 2 (day 8-14) (n, Δ in score ± SE)	201 -75.2 ± 4.8	23 -86.6 ± 17.2	98 -58.7 ± 6.0	<0.001	0.026	0.089
Week 3 (day 15-21) (n, Δ in score ± SE)	192 -82.4 ± 5.2	23 -109 ± 17.2	97 -63.0 ± 6.8	0.005	0.033	0.163
Week 4 (day 22-28) (n, Δ in score ± SE)	191 -90.8 ± 5.2	23 -108 ± 16.8	95 -70.8 ± 6.8	<0.001	0.121	0.220

[1]FP=Fluticasone propionate. [2]SE=Standard Error. P-values at pre-treatment (Days -6 to 0) were based on mean scores at baseline, and at subsequent visits p-values were based on mean absolute change from baseline using the F-test.

9.3. Comparability of qd and bid Dosing of FP Nasal Spray

An important review issue for approval of FP Nasal Spray for the NAPR indication in adults and children was demonstration of a linkage for the PAR studies that examined comparability between FP 100 µg bid and FP 200 µg qd. Two studies-FLN 310 and FLN 311 examined these 2 doses of FP Nasal Spray and compared efficacy for these 2 dosing regimens to placebo treatment. While statistically insignificant differences were not always noted between the 2 FP dosing regimens, numerically the differences in the primary efficacy endpoint (the patient self-rated daily reflective TNSS), along with the secondary efficacy endpoints were minimal and the 2 dosing regimens were considered to be comparable with regard to efficacy in these 2 studies. Analysis of the end-of-dosing interval (or duration of drug effect) was assessed by the a.m. nasal obstruction score which showed that for both study FLN 310 and FLN 311, the FP bid dosing regimen was numerically slightly better at decreasing this score than the FP qd regimen, though no statistically significant difference between these 2 treatments was seen throughout the 24 week period of the studies, with the exception of weeks 1-6 of the double-blind treatment period in study FLN

310. Formal analysis of onset of efficacy for the 2 FP doses vs. placebo was not evaluated in either of these 2 PAR studies.

9.4. Onset of Action

Onset of action was evaluated in 2 'onset of action' park studies specifically designed to address this endpoint, along with a pivotal rhinitis trial from NDA 20-121 (Study FLN-203) which evaluated a 12 hour time point post-initiation of treatment with FP Nasal Spray. Based on these 3 studies, a 12 hour onset of action of FP Nasal Spray at a dose of 200 μg qd, as defined by a sustained statistically significant reduction in TNSS compared to placebo treatment, was seen (see Section 8.3. of the medical officer review).

10.0. Integrated Summary of Safety

The clinical experience and safety database with FLONASE Aqueous Nasal Spray is considerable, both from clinical trials and from marketing exposure. Clinical trial data supported FDA approval of FLONASE (NDA 20-121) as a safe and effective treatment of nasal symptoms of SAR and PAR in adults and adolescents 12 years of age and older on 10/19/94. Additionally, FLONASE has been approved for the treatment of nasal symptoms of SAR and PAR in pediatric patients age 4-11 (efficacy supplement to NDA 20-121, approved 10/31/97). FLONASE was first marketed worldwide in 1991 (in the U.K., for SAR in adults) and has been marketed in the U.S. since 01/95.

Safety data from the original NDA (20-121) will not be reiterated in this review, the focus of which will be integration of safety data from the 3 NAPR studies conducted in patients 12 years of age and older, submitted to this efficacy supplement (studies FLN 350, FLN 351, and FLTA 3010), in order to confirm no new safety concerns with FLONASE Aqueous Nasal Spray. Hence, this safety analysis will consist of an overview of patient withdrawals, pooled adverse event frequencies (along with 'serious' adverse events), laboratory results and physical exam findings, based on the intent-to-treat population from the 3 NAPR studies.

Longer-term safety data in this ISS will come from one, U.S. (FLTA 3010) 6-month open label safety extension in which 289 patients completed the open label period of the study.

10.1. Extent and Duration of Exposure

For the 3 NAPR studies (FLN 350, FLN 351, and FLTA 3010), a total of 1191 patients were enrolled in the clinical trials, of whom 937 patients were treated with FP Nasal Spray during double-blind and open-label treatment combined and 326 patients were treated with placebo. Of these 937 patients, 195 patients received FP Nasal Spray for at least 184 days (~ 6 months), with some patients continuing treatment for up to 237 days (~ 8 months). These data are presented on pages 12 and 65 of Vol. 38 of the sponsor's efficacy supplement submission [NDA 20-121, S-009, 38:12, 65].

The total duration of exposure of each dose of FP Nasal Spray during the double-blind and open-label treatment period is presented in Table I below.

Based on these data, the FP 200 µg bid dose patients received the longest duration of treatment with FP Nasal Spray, with 124 patients receiving at least 184 days of treatment and 19 of these patients treated with FP 200 µg bid between 213 and 237 days.

Table I. Patient Exposure to FLONASE Nasal Spray:
All NAPR Studies: FLN 350, FLN 351, and FLTA 3010
[NDA 20-121, S-009, 38:65-66]

Treatment Group	# of Pts Exposed	Days 1-14	Days 15-28	Days 29-42	Days 43-61	Days 62-122	Days 123-183	Days 184-212	Days 213-237
Placebo	326	8	173	145	0	0	0	0	0
FP 50 µg bid	208	16	141	51	0	0	0	0	0
FP 100 µg bid	332	12	176	143	1	0	0	0	0
FP 200 µg bid	538	14	128	128	12	23	109	105	19

10.2. Patient Demographics

A total of 1191 patients were enrolled in the NAPR trials, of whom 289 participated in the open label safety extension of study FLTA 3010. Demographic data from the double-blind treatment period of the 3 NAPR studies are presented in Table II below.

Table II. Patient Demographics in the 3 NAPR Studies
[NDA 20-121, S-009, 38:14, 70]

	Double-blind Treatment Period					Open-Label Period
	Placebo (n-326)	FP 50 µg bid (n=208)	FP 100 µg bid (n=332)	FP 200 µg bid (n=325)	Total (n=1191)	FP 200 µg bid (n=289)
Gender: overall p-value=0.275						
Female	201	142	203	213	759 (64%)	189 (65%)
Male	125	66	129	112	432 (36%)	100 (35%)
Age (years): overall p-value=0.155						
Mean	43.1	42.7	41.8	40.6	42.1	43.3
Range	12-79	14-86	12-83	12-75	12-86	14-79
Ethnic Origin: overall p-value=0.541						
Caucasian	313	195	310	308	1126 (95%)	280 (97%)
Black	4	4	12	10	30 (3%)	1 (<1%)
Hispanic	8	8	9	4	29 (2%)	7 (2%)
Other	1	1	1	3	6 (<1%)	1 (<1%)
Duration of NAPR (years): overall p-value=0.581						
1-4 years	84	48	77	85	294 (25%)	63 (22%)
5-9 years	65	44	91	70	270 (23%)	77 (27%)
10-14 years	63	38	57	63	221 (19%)	52 (18%)
≥ 15 years	114	78	107	107	406 (34%)	97 (34%)

Based on the patient demographic characteristics delineated in Table I for all 3 NAPR studies, no significant differences were noted between the 4 different treatment groups (3 different FLONASE doses and placebo). Approximately 2/3 of patients in all 4 treatment groups were female, and the majority of all patients (male and female) were Caucasian, with a mean age of 42.1 years, and ≥ a 15 year history of NAPR. Likewise, no significant different in patient demographics were noted between the double-blind and open-label treatment periods.

10.3. Patient Disposition

The patient disposition for the 3 NAPR studies combined is presented in Table III below. Based on these data, the reasons for patient withdrawal were generally similat across treatments, with no more than 10% of patients withdrawing for any reason for the double-blind treatment period, but a higher number (23%) withdrawing during the long-term safety extension of FLTA 3010. No overwhelming reason predominated for patient withdrawal, though a slightly greater incidence of adverse events, accounting for patient withdrawal was noted.

Table III. Patient Disposition for all 3 NAPR Studies [NDA 20-121, S-009, 38:15, 73]

Patient Disposition	Double-blind Treatment Period				Open-label Treatment Period
	Placebo	[1]FP 50 µg bid	FP 100 µg bid	FP 200 µg bid	FP 200 µg bid
Number enrolled	326	208	332	325	289
Number (%) Withdrawn	18 (6%)	20 (10%)	20 (6%)	16 (5%)	66 (23%)
Reasons for Withdrawal					
Adverse Event	9 (3%)	6 (3%)	6 (2%)	5 (2%)	18 (6%)
Failed to meet entrance criteria	2 (<1%)	5 (2%)	5 (2%)	3 (<1%)	1 (<1%)
Failed to return	0 (0%)	2 (<1%)	3 (<1%)	4 (1%)	19 (7%)
Lack of efficacy	3 (<1%)	2 (<1%)	4 (1%)	0 (0%)	11 (4%)
*Other	4 (1%)	5 (2%)	2 (<1%)	4 (1%)	17 (6%)

[1]FP 50 µg bid treatment only used in FLTA 3010.
*Other reasons for withdrawal include: withdrawal of consent, protocol violation.

10.4. Adverse Event Frequency

Review of adverse events (AEs) experienced by patients in the 3 different FP treatment groups (50 µg bid, 100 µg bid, and 200 µg bid) and in the placebo group, revealed similar AE frequencies. Similar to the current labeling for FLONASE Nasal Spray, headache, throat irritation, epistaxis, upper respiratory tract infection, nasal irritation, and cough were the most common adverse events, with epistaxis being more common in the FP treatment groups, followed by headache. Of note, similar safety profiles were demonstrated for the FP 100 µg bid and FP 200 µg bid treatments. The most common AE leading to patient withdrawal from the study was epistaxis (15 cases) [NDA 20-121, S-009, 38:29-30].

Subgroup analysis of AEs for the 3 NAPR studies revealed no gender difference in the types of AEs reported between males and females, though female patients did report a slightly higher overall frequency of AEs (range of: 50-55% across all treatment groups) compared to male patients (range of: 34-45% across all treatment groups) [NDA 20-121, S-009, 38:20].

When examined across different age groups, defined as: ≤ 16 years of age, 17-64 years of age, and ≥ 65 years of age, the percentage of patients experiencing

AEs similar amongst the 3 different age groups [NDA 20-121, S-009, 38:21]. For the patient age group 65 years of age, the most common AEs included epistaxis, headaches, and throat irritation, which was similar to the population as a whole. For the age 12-16 population, which comprised only 51 patients total (4% of all NAPR patients), the most common AEs consisted of headache, URI, epistaxis, viral respiratory infection, and cough [NDA 20-121, S-009, 38:21]. Again, these AEs were similar to events seen in the overall patient population. Importantly, the number of patients in both of these age groups were too small to draw conclusions regarding incidence of AEs by treatment group.

Adverse event frequency by ethnic origin is somewhat difficult to interpret, as 95% of all patients evaluated in the 3 NAPR studies were Caucasian. The number of patients in the other ethnic groups are again too small to draw conclusions. Nonetheless, for the Caucasian group, the most frequent AEs consisted of headaches, epistaxis, throat irritation, and URI; again similar to the AE profile for the total population of NAPR patients [NDA 20-121, S-009, 38:21].

Table IV: Adverse Event Frequency ≥ 1% for NAPR Studies (FLN 350, 351 and FLTA 3010) [NDA 20-121, S-009, 38:17, 74-133]

Adverse Event	Placebo (n=326)	FP 50 µg bid (n=208)	FP 100 µg bid (n=332)	FP 200 µg bid (n=325)
Any AE	143 (44%)	99 (48%)	170 (51%)	160 (49%)
Headache	34 (10%)	34 (16%)	48 (14%)	59 (18%)
Throat irritation	24 (7%)	9 (4%)	30 (9%)	29 (9%)
Epistaxis	14 (4%)	19 (9%)	27 (8%)	28 (9%)
URI	22 (7%)	10 (5%)	22 (7%)	24 (7%)
Nasal irritation	11 (3%)	10 (5%)	14 (4%)	9 (3%)
Cough	9 (3%)	13 (6%)	17 (5%)	11 (3%)
Dryness of nose	3 (< 1%)	3 (1%)	7 (2%)	3 (< 1%)
Ear signs and symptoms	3 (< 1%)	4 (2%)	5 (2%)	3 (< 1%)
Nasal itching	2 (< 1%)	3 (1%)	0 (0%)	1 (< 1%)
Laryngitis	2 (< 1%)	3 (1%)	0 (0%0	0 (0%)
Dizziness	3 (< 1%)	4 (2%)	3 (< 1%)	1 (< 1%)
Nausea and vomiting	6 (2%)	7 (3%)	8 (2%)	9 (3%)
Diarrhea	3 (< 1%)	6 (3%)	5 (2%)	7 (2%)
GI signs and symptoms	3 (< 1%)	5 (2%)	2 (< 1%)	3 (< 1%)
Viral GI infections	3 (< 1%)	0 (0%)	1 (< 1%)	4 (1%)
Viral respiratory infections	6 (2%)	3 (1%)	9 (3%)	9 (3%)
Temperature regulation disturbances	4 (1%)	4 (2%)	7 (2%)	3 (< 1%)
Malaise and fatigue	1 (< 1%)	3 (1%)	6 (2%)	5 (2%)
Pain	2 (< 1%)	1 (< 1%)	6 (2%)	4 (1%)
Muscle pain	3 (< 1%)	0 (0%)	4 (1%)	3 (< 1%)
Eye irritation and itching	2 (< 1%)	4 (2%)	2 (< 1%)	0 (0%)
Menstruation symptoms	1 (< 1%)	2 (1%)	2 (< 1%)	4 (2%)

When long-term exposure (i.e. up to 6 month) of adults and adolescents to twice daily FP Nasal Spray 200 μg bid was assessed for the 289 patients in the safety extension of FLTA 3010, 232 (77%) of whom completed the 6 month trial, AEs during this period were similar to those reported in the shorter double-blind treatment period, though the incidence of epistaxis was somewhat higher. The incidence of epistaxis during the open-label period for a treatment dose of FP 200 μg bid was 14% vs. 8% for the 28 day double-blind treatment period at a treatment dose of FP 100 μg bid. Important to note when evaluating this discrepancy was the higher dose of FP Nasal Spray utilized during the open-label period which also could have contributed to the higher frequency of AEs such as epistaxis during the open label treatment period [NDA 20-121, S-009, 38:23].

Analysis of the AE frequency for evidence of a possible dose response with FP Nasal Spray treatment (50 μg bid, vs. 100 μg bid, and 200 μg bid) in NAPR failed to support an AE dose response (see Table IV above).

A comparison of the adverse event profile from the NAPR clinical trials and the approved package insert for FP Nasal Spray (SAR and PAR indication in children and adults), indicates that the AE frequencies for FP Nasal Spray were similar. Epistaxis was reported by a slightly higher % of patients in the NAPR studies (8-9%) than in the SAR/PAR studies (6-7%) used to support initial approval of FLONASE Nasal Spray, and than in patients treated with placebo (4%), but the frequency of most other AEs was comparable to the placebo group. In addition, because of minor differences in coding dictionaries used to examine the integrated sets of data, the AE profile for the NAPR studies captured AE frequencies for throat irritation and upper respiratory tract infections, whereas these 2 AEs were not categorized in the studies used to support the current approved label for FLONASE Nasal Spray [NDA 20-121, S-009, 38:32]. The frequency of these 2 AEs in the NAPR studies were very similar between FP treatment and placebo.

Nonetheless, the AE profiles for the NAPR studies and the currently approved label are so similar that no revision of the existing AE section of the package insert in considered necessary by the medical reviewer to address the AE incidence observed with FP 200 μg qd in the 3 NAPR studies.

10.5. Serious Adverse Events

For the double-blind treatment period for the 3 NAPR studies, serious adverse events were reported for < 1% of patients (6/1191): one on placebo, 4 on FP 100 μg bid, and one on FP 200 μg bid [NDA 20-121, S-009, 38:26]. Of these 6 patients, one FP 100 μg bid patient (patient # 12863) died from coronary atherosclerosis which was unrelated to study medication. Serious AEs in the other 5 patients (patient # 13239: anxiety, patient # 12252: intestinal obstruction, patient #77: abdominal discomfort with fever, chills, flank pain, urosepsis, prostatitis, and gout, patient # 276: exacerbation of metastatic prostate cancer with

resultant orchiectomy, and patient #252: ovarian cyst) were also considered by the principal investigator not to have been related to study medication [NDA 20-121, S-009, 38:146-148]. Furthermore, only one of these 5 patients withdrew from the study due to serious AEs: patient #77, who experienced urosepsis due to E. coli, prostatitis, and gout, none of which were considered to be related to study medication.

For the open label period, serious AEs were reported in 1% (4/289) of patients. The 4 reports of serious AEs involved one case of chronic cystitis in the setting of transitional cell carcinoma of the bladder (patient # 12241), one case of chest pain (patient # 13371), one case of ruptured ectopic pregnancy (patient # 13444), and one case of cholecystectomy (patient # 12405) [NDA 20-121, S-009, 38:149-151]. Again, none of these AEs were considered to be related to study medication.

A total of 3 patients became pregnant during the 3 NAPR studies, all during study FLTA 3010. Two patients had positive pregnancy tests during the double-blind treatment period and one during the open-label safety extension [NDA 20-121, S-009, 38:30, 172]. One of the 3 patients (# 13444) experienced a ruptured ectopic pregnancy which was considered unrelated to study medication, another had an elective abortion, and the outcome of the 3rd pregnancy is unknown.

10.6. Laboratory Tests

Review of laboratory tests for both the double-blind and open-label periods by shift tables and clinically significant changes for the 3 NAPR studies revealed few patients with significant laboratory abnormalities (<1% for the double-blind period and ≤ 4% for the open-label period). Overall changes in laboratory tests tended to be minor, with no trends detected [NDA 20-121, S-009, 38:187-198].

10.6.1. Tests of HPA Axis in the NAPR Studies

The potential for adrenal suppression was evaluated in the 3 NAPR studies via the measurement of a.m. plasma cortisol levels (all 3 studies), and via short Cosyntropin testing after 28 days of double-blind treatment, and after 6 months of open-label treatment with FP 200 μg bid in study FLTA 3010. A clinically significant abnormality in adrenal response was defined by the sponsor as: (1) an a.m. plasma cortisol level < 5 μg/dL, (2) a baseline a.m. plasma cortisol level prior to Cotrosyn stimulation testing of ≤ 5 μg/dL, (3) an increase of < 7 μg/dL in plasma cortisol level post-Cortrosyn stimulation, and (4) a plasma cortisol level of < 18 μg/dL, post-stimulation with Cortrosyn [NDA 20-121, S-009, 38:34].

A list of all patients exhibiting an abnormal adrenal response during performance of either of the 3 NAPR studies is provided by the sponsor on page 35 of Vol. 38 of the efficacy supplement [NDA 20-121, S-009, 38:35]. Based on these data, ~ 1% (12 patients: 2 in the placebo group, 3 in the FP 50 μg bid group, 3 in the FP 100 μg bid group, and 4 in the FP 200 μg bid group) of all patients

had plasma cortisol concentrations below 5 μg/dL prior to and during the double-blind treatment period. No patient in the open-label period had an a.m. plasma cortisol level < 5 μg/dL during open label treatment with FP 200 μg bid. Again, there was no evidence of a dose response with the 3 different doses of FP Nasal Spray, though the FP 200 μg bid group did exhibit a slightly higher number of patients with a significantly lower a.m. plasma cortisol than the other 3 treatment groups.

Results of Cortrosyn testing during the open-label period were previously discussed in the medical officer review of FLTA 3010 but will be summarized briefly in this section. Importantly, prospective patients for the open-label portion of FLTA 3010 were not required to have a normal response to Cotrosyn stimulation testing at the end of the double-blind treatment period (Visit 4) in order to be eligible to enroll into the open-label portion of the study. Nonetheless, the % of patients with any Cortrosyn stimulation abnormality at Visit 4 was similar across the 4 treatment groups. The % of patients with any Cortrosyn stimulation test abnormality at Visit 10 (after 6 months of open-label treatment) was similar to that at the end of the 4 week double-blind treatment period, with the exception of more patients in the post-6 month treatment period having a post-stimulation increase in plasma cortisol of < 7 μg/dL (18% (39 of 22 patients) vs. 10% (27 of 279 patients)) than after 4 weeks of treatment [NDA 20-121, S-009, 38:36]. Post-stimulation plasma cortisol levels < 18 μg/dL were seen in 4% of patients (11 total) after 4 weeks of treatment with FP Nasal Spray, and for 3% of patients (7 total) after 6 months of treatment with FP Nasal Spray. Three (3) % of patients (8 total) after 4 weeks of treatment and 2% of patients (5 total) after 6 months of treatment had both a post-stimulation change < 7 μg/dL and a post-stimulation cortisol < 18 μg/dL [NDA 20-121, S-009, 38:36-37, 185-186]. Only one patient (#11560) had both abnormalities after both 4 weeks and then 6 months of treatment with FP Nasal Spray. A summary of Cortrosyn-stimulation test results for study FLTA 3010 are presented in Table V. below.

Table V. Cortrosyn-Stimulation Data for NAPR Study FLTA 3010
[NDA 20-121, S-009, 38:36, 185-186]

	Post-Week 4: Final double-blind visit and baseline for open label period				Post-Month 6
Cortisol Values	**Placebo**	**FP 50 µg bid**	**FP 100 µg bid**	**FP 200 µg bid**	**6 months of Rx with FP 200 µg bid, preceded by the previous double-blind assignment (FP 50 µg, 100 µg, or 200 µg bid)**
Baseline a.m. cortisol ≤ 5 µg/dL			1 (1%)	2 (3%)	1 (2% placebo) 1 (2% FP 100 µg bid)
Post-Cortrosyn stimulation change < 7 µg/dL	6 (9%)	8 (12%)	8 (12%)	5 (7%)	3 (5% placebo) 11 (21% FP 50 µg bid) 17 (28% FP 100 µg bid) 8 (15% FP 200 µg bid)
Post-Cortrosyn stimulation value < 18 µg/dL	4 (6%)	2 (3%)	2 (3%)	3 (4%)	2 (4% FP 50 µg bid) 4 (7% FP 100 µg bid) 1 (2% FP 200 µg bid)

In summary, results of adrenal responsiveness, as based on the 4 week and 6 month treatment period in study FLTA 3010, support the conclusion that a.m. plasma cortisol levels and Cortrosyn stimulation tests were not significantly affected by FP Nasal Spray treatment. In addition, strong evidence of a dose response in either of the 2 measures of adrenal function was not apparent, based on this one study.

10.7. Physical Exam Findings

Routine physical exams performed during the NAPR studies failed to reveal any remarkable findings. Specifically with respect to the ENT exam, a total of 5 cases of oral candidiasis were detected in patients receiving FP Nasal Spray out of the sum total of 937 patients treated with FP Nasal Spray during the double-blind and open-label period for all 3 NAPR studies (4 patients in study FLTA 3010: 2 patients were treated with FP 50 µg bid and 2 patients were treated with FP 200 µg bid; and 1 patient in FLN 350 treated with FP 200 µg bid).

With regard to incidence of nasal ulcerations or nasal septal perforations in the 3 NAPR studies, a total of 2 patients (both receiving FP 200 µg bid, and both in study FLTA 3010) developed nasal septal ulcerations, 1 patient (on FP 100 µg bid, in study FLN 351) developed a nasal ulceration, 1 patient (on FP 100 µg bid, in study FLTA 3010) developed a nasal septal perforation, and 1 patient (on FP 100 µg bid, in study FLN 351) developed a nasal septal perforation. In summary, a total of 5 nasal mucosal ulceration-type events were detected in the 3 NAPR trials, either by physical exam or by patient adverse event reporting, followed by physical exam.

10.8. Vital Signs

Vital signs were not specifically evaluated in this efficacy supplement and potential abnormalities were not tabulated. Nonetheless, based on clinical safety data from NDA 20-121, and the mechanism of action of FLONASE, there is no reason to suspect that this medication would significantly alter hemodynamics of patients taking this medication.

10.9. 12-Lead ECGs

12-lead ECGs were not specifically evaluated in this efficacy supplement and will not be addressed in this review.

10.10. Special Populations

None of the NAPR studies for the efficacy supplement to NDA 20-121 were conducted in renally or hepatically impaired subjects, nor was FLONASE Nasal Spray studied in any special populations in the original NDA for FLONASE. Hence no information regarding FLONASE dosing in these 2 special populations is currently available and the label for the NAPR indication will not result in any changes to the current label.

11.0. Data Verification (DSI Audit)

A Division of Scientific Investigations (DSI) audit of the clinical data for either of the NAPR studies: FLN 350, FLN 351, or FLTA 3010 was not required for efficacy supplement approval as this was a prerequisite of NDA approval of FLONASE Aqueous Nasal Spray under NDA 20-121. Hence, auditing of clinical study sites was not performed.

12.0. CONCLUSION: Executive Summary of Efficacy and Safety

Evaluation of the efficacy of FLONASE Aqueous Nasal Spray for the NAPR indication in adults 12 years of age and older and in children 4-11 years of age was based on the analysis of 3 NAPR clinical trials performed in adult patients (FLTA 3010, FLN 350, and FLN 351), one of which was considered to be pivotal (FLTA 3010) in which FP 100 μg bid was evaluated. Review of primary and secondary efficacy endpoints demonstrated efficacy of FLONASE Nasal Spray in decreasing nasal symptoms of NAPR, compared to placebo treatment. Linkage of these NAPR efficacy data to 2 PAR studies (FLN 310 and FLN 311) was performed and established the comparability of FP 100 μg bid to FP 200 μg qd. Extension of these adult data was performed by utilization of the pediatric rule, whereby no significantly different pathophysiology was expected between SAR/PAR and NAPR and data demonstrating efficacy in children age 4-11 years was available for the SAR/PAR indication.

FLONASE Nasal Spray demonstrated adequate duration of effect, as per analysis of the a.m. nasal obstruction score—the only end-of-dosing interval measurement performed in the 3 NAPR studies. Analysis of the onset of efficacy was not formally performed in the 3 NAPR trials, although a statistically

significant decrease in total nasal symptoms was noted for the FLONASE 200 µg dose in 2 'onset of action' park studies and in SAR study FLN 203 (reviewed in the original NDA for FLONASE, NDA 20-121), compared to placebo at 12 hours post-dosing

Analysis of response of NAPR symptoms to treatment separately by week 1 and week 2, revealed that FLONASE Aqueous Nasal Spray generally achieved a statistically significant reduction in many efficacy endpoints by week 1 of treatment but continued to provide a greater numerical reduction in NAPR symptoms by week 2 of treatment and thereafter.

Extensive subgroup analyses by race, gender, and age were not attempted by the sponsor for this efficacy supplement.

The safety database for FLONASE Aqueous Nasal Spray consisted of 937 safety evaluable patients in the 3 NAPR trials, of which 195 received FP Nasal Spray for at least 184 days (~ 6 months), with some patients continuing treatment for up to 237 days (~ 8 months).

Overall, FLONASE Aqueous Nasal Spray was safe and well-tolerated given at a dose of 50 µg, 100 µg, and 200 µg twice a day. No serious adverse events occurred in patients treated with FLONASE Nasal Spray, and only one death was reported due to coronary atherosclerosis which was not due to study medication. Similar to placebo treatment, headache was the most common adverse event, followed by throat irritation, and epistaxis. No clinically significant trends in laboratory abnormalities were demonstrable in FP Nasal Spray treated patients and no obvious difference in outlier values was noted between the various treatment groups. Follow-up physical examinations post-treatment in all 3 FP treatment groups were generally consistent with an unremarkable exam or one in which findings of rhinitis (e.g. nasal turbinate swelling, post-nasal drip) were demonstrable. A few rare reports of nasal ulceration and oral candidiasis were reported in FP treated patients, primarily at the FP 200 µg bid dose, but the incidence of these events was < 0.01%. In summary, FLONASE Aqueous Nasal Spray appears to be safe for the treatment of symptoms of NAPR (including nasal obstruction) at the recommended dose of 200 µg qd or 100 µg bid in adult patients age 12 years and older or 100 µg qd in pediatric patients (age 4-11 years) with the appropriate adjustment in dose (to a maximum daily dose of 200 µg qd) for adequate nasal symptom control.

12.1. Reviewer Recommendation:

FLONASE Aqueous Nasal Spray is shown to be safe and effective for the treatment of symptoms of non-allergic perennial rhinitis (NAPR) (including nasal obstruction) in adults ≥ 12 years of age. By extension of the pediatric rule based on prior approval of the SAR and PAR indication in children, FLONASE Aqueous Nasal Spray is also felt to be safe and effective for the treatment of symptoms of non-allergic perennial rhinitis (NAPR) (including nasal obstruction)

in children 4-11 years of age. The recommended dose is 200 µg once a day (two 50 µg sprays in each nostril once a day) or 100 µg twice a day (one 50 µg spray in each nostril twice a day) in adult patients age 12 years and older and 100 µg once a day (one 50 µg spray in each nostril once a day), with increase in dosage to 200 µg once a day if no clinical response is seen with the 100 µg once a day dose in children age 4-11 years of age. As per the current pediatric labeling for FLONASE Aqueous Nasal Spray, the recommendation to decrease the 200 µg once a day dose in children age 4-11 years of age for unresponsive nasal symptoms of NAPR to the 100 µg once a day dose once symptoms improve is also a recommendation for the NAPR indication in children age 4-11 years. The medical reviewer of the efficacy supplement to NDA 20-121 recommends approval of FLONASE Aqueous Nasal Spray for these clinical indications.

13.0. Labeling Comments

The sponsor's proposed label for FLONASE Nasal Spray (with inclusion of the NAPR indication) was reviewed by the medical officer. Overall, few changes were made to the currently approved label, although the following comments were offered by the reviewing medical officer for label revision. (Note: all additions are marked in **'bold-type'** and all deletions are marked in 'strike-out'):

(1) Page 15, 2nd paragraph of the sponsor's FLONASE Nasal Spray label change submission, 'Clinical Trials' section:

Three randomized, double-blind, parallel, vehicle-controlled trials were conducted in 1,191 patients with perennial nonallergic rhinitis. These trials evaluated the patient-rated total nasal symptoms scores (nasal obstruction, postnasal drip, rhinorrhea) in patients treated for 28 days of double-blind therapy and **in one of the 3 trials for** 6 months of open-label treatment. **Two of these trials demonstrated** [redacted] that patients treated with FLONASE Nasal Spray at **a dose of 100 mcg twice daily** [redacted] exhibited statistically significant decreases in total nasal symptoms scores compared with patients treated with vehicle.

(2) Page 15, 4th paragraph of the sponsor's FLONASE Nasal Spray label change submission, 'Individualization of Dosage' section:

Individual patients will experience a variable time to onset and different degree of symptom relief. [redacted] **a decrease in nasal symptoms in treated subjects compared to placebo was shown to occur as soon as 12 hours after treatment with a 200 mcg dose of FLONASE Nasal Spray.**

APPENDIX I: ONSET OF ACTION STUDIES

Summaries of additional efficacy and safety data for each of these 22 studies are provided in Section 2.IV of this supplemental NDA. These studies are described below and in Section 2.I.

Onset of Effect (Park) Studies in Seasonal Allergic Rhinitis in Adolescents and Adults

Protocol	Study Design	Duration of Treatment	Dose	Number of Patients
FLN-444	park study DB, PC, PG, R	7 days	Placebo BDP 168mcg BID FP 200mcg QD	102 103 104
FLN-445	park study DB, PC, PG, R	7 days	Placebo BDP 168mcg BID FP 200mcg QD	106 107 106

DB = double-blind; PC = placebo-controlled; PG = parallel-group; R = randomized
FP=fluticasone propionate aqueous nasal spray; BDP=beclomethasone diproplonate aqueous nasal spray

Other Studies in Seasonal Allergic Rhinitis in Adolescents and Adults

Protocol	Study Design	Duration of Treatment	Dose	Number of Patients
FLN-203	DB, PC, PG, R	14 days	Placebo FP 100mcg BID FP 200mcg QD	75 75 77
FLN-204 (excluding Paull)	DB, PC, PG, R	28 days	Placebo FP 100mcg BID FP 200mcg QD	70 70 71
FLN-230	DB, PC, PG, R	14 days	Placebo oral fluticasone propionate 5mg QD oral fluticasone propionate 10mg QD FP 200mcg QD	77 73 77 77
FLN-270	DB, PC, PG, R	28 days	Placebo FP 200mcg QD (old) FP 200mcg QD (new)	99 104 101
FLN-301 (excluding Paull)	DB, PC, PG, R	14 days	Placebo BDP 168mcg BID FP 200mcg QD	77 78 80
FLN-305	DB, PC, PG, R	14 days	Placebo FP 100mcg BID FP 200mcg QD	81 73 89
FLN-306	DB, PC, PG, R	28 days	Placebo BDP 168mcg BID FP 100mcg BID FP 200mcg QD	58 61 64 55
FLN-401	DB, DD, PC, PG, R	14 days	Placebo terfenadine 60mg BID FP 200mcg QD	77 77 78

DB = double-blind; DD=double-dummy; PC = placebo-controlled; PG = parallel-group; R = randomized
FP=fluticasone propionate aqueous nasal spray; BDP=beclomethasone diproplonate aqueous nasal spray

Other Studies in Seasonal Allergic Rhinitis in Adolescents and Adults (continued)

PROTOCOL	STUDY DESIGN	DURATION OF TREATMENT	DOSE	NUMBER OF PATIENTS
FLN-402	DB, DD, PC, PG, R	28 days	Placebo terfenadine 60mg BID FP 200mcg QD	115 116 117
FLN-411	DB, DD, PC, PG, R	14 days	Placebo astemizole 10mg QD FP 200mcg QD	106 102 105
FLN-412	DB, DD, PC, PG, R	28 days	Placebo astemizole 10mg QD FP 200mcg QD	102 100 102
FLTA4004	DB, DD, PC, PG, R	28 days	Placebo loratadine 10mg QD FP 200mcg QD	112 112 109
FLTA4006	DB, DD, PC, PG, R	14 days	Placebo loratadine 10mg QD FP 200mcg QD loratadine 10mg QD plus FP 200mcg QD	150 150 150 150
FLTA4024	DB, DD, PC, PG, R	14 days	Placebo loratadine 10mg QD FP 200mcg QD loratadine 10mg QD plus FP 200mcg QD	164 166 161 164

DB = double-blind; DD=double-dummy; PC = placebo-controlled; PG = parallel-group; R = randomized
FP=fluticasone propionate aqueous nasal spray; BDP=beclomethasone dipropionate aqueous nasal spray

Studies in Seasonal Allergic Rhinitis in Pediatric Patients

PROTOCOL	STUDY DESIGN	DURATION OF TREATMENT	DOSE	NUMBER OF PATIENTS
FLN-320	DB, PC, PG, R	14 days	Placebo FP 100mcg QD FP 200mcg QD	85 84 81
FLN-321	DB, PC, PG, R	14 days	Placebo FP 100mcg QD FP 200mcg QD	83 83 83

DB = double-blind; PC = placebo-controlled; PG = parallel-group; R = randomized
FP=fluticasone propionate aqueous nasal spray

Studies in Perennial Allergic Rhinitis in Adolescents and Adults

PROTOCOL	STUDY DESIGN	DURATION OF TREATMENT	DOSE	NUMBER OF PATIENTS
FLN-310	DB, PC, PG, R	180 days	Placebo FP 100mcg BID FP 200mcg QD	116 121 128
FLN-311	DB, PC, PG, R	180 days	Placebo BID BDP 168mcg BID FP 100mcg BID FP 200mcg QD	113 116 119 118

DB = double-blind; PC = placebo-controlled; PG = parallel-group; R = randomized
FP=fluticasone propionate aqueous nasal spray; BDP=beclomethasone dipropionate aqueous nasal spray

Studies in Perennial Nonallergic Rhinitis in Adolescents and Adults

PROTOCOL	STUDY DESIGN	DURATION OF TREATMENT	DOSE	NUMBER OF PATIENTS
FLN-351	DB, PC, PG, R	28 days	Placebo FP 100mcg BID FP 200mcg BID	93 98 95
FLTA3010	DB, PC, PG, R	28 days	Placebo FP 50mcg BID FP 100mcg BID FP 200mcg BID	210 208 211 208

DB = double-blind; PC = placebo-controlled; PG = parallel-group; R = randomized

FEB 5 1998

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

Application #:	NDA 20-121	Application Type:	Efficacy Supplement
Sponsor:	Glaxo-Wellcome, Inc.	Product/Proprietary Name:	Flonase Nasal Spray
Principal Investigator:	None	USAN/Established Name:	Fluticasone Propionate Aqueous Nasal Spray
Category of Drug:	Corticosteroid	Route of Administration:	Intranasal
Reviewer:	Alexandra S. Worobec, M.D.	Review Date:	01/26/98

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
12/17/97	12/18/97	Efficacy Supplement	45 Day Clinical Review

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
07/31/95	NDA 20-625	NDA Application for ALLEGRA

Overview of Application/Review: This is an efficacy supplement for Flonase Aqueous Nasal Spray 50 mcg/actuation for the indication of non-allergic perennial rhinitis (NAPR) in adults and children age 4 years and older. The recommended dose in adults will be 200 mcg qd or 100 mcg bid, with tapering to 100 mcg qd, as tolerated. The recommended dose in children will be 100 mcg qd, with increase to 200 mcg (or 100 mcg bid), if necessary for control of symptoms. The submission consists of 3 pivotal NAPR studies performed in adults, which will be bridged to 2 PAR studies previously reviewed for approval for the PAR indication in adults and adolescents in NDA 20-121 using principles outlined in the Pulmonary Division's 'Points to Consider' guidelines of January 1996 in order to demonstrate clinical comparability between bid and qd dosing of Flonase for the treatment of NAPR symptoms. Since Flonase is already approved for the SAR and PAR indication in children age 4 years and older, and the clinical course of NAPR and the safety profile of Flonase suggest that it should not be necessary to introduce a distinction between allergic and non-allergic causality in this patient population. Based on a review of the onset of action data (medical officer review, NDA 20-121) from the Flonase NDA, the Division has determined that the sponsor will need to submit information regarding the onset of action of Flonase to support a 12 hour onset of action claim (to be submitted to the Agency by 02/98.

Outstanding Issues: No filing issues. Two outstanding review issues consist of: (1) the onset of action of intranasal Flonase and (2) cross-study comparability between the 3 NAPR studies and the 2 PAR studies which form the basis for approval for the NAPR indication. Preliminary review of the clinical trial design of the 3 NAPR studies and the 2 PAR studies indicates that while some differences in trial design are present, these should not be problematic, provided that statistically significant efficacy for the Flonase treatment groups are demonstrated in the NAPR studies, vs. placebo treatment.

Recommended Regulatory Action: Efficacy supplement is fileable and review may proceed.

N drive location:

New Clinical Studies: _____ Clinical Hold _____ Study May Proceed

NDAs:

Efficacy/Label Supp.:	Approvable	Not Approvable
Signed: Medical Reviewer:	/S/	Date: 02/04/98
Medical Team Leader:	/S/	Date: 2/5/98

APPEARS THIS WAY
ON ORIGINAL

I. NDA Filing:

As discussed in the 21-day filing meeting for the efficacy supplement for NDA 20-121 Flonase Nasal Spray, 50 mcg/actuation, dated 01/14/98, this NDA is deemed complete and can be filed from a clinical standpoint. The sponsor, will however need to submit onset of action data to support its labeling claims "of onset of action within 12 hours of dosing", which is anticipated to be submitted to the Agency by the sponsor by 02/98. As documented in a fax to the sponsor from the Pulmonary Division (Dr. Robert Meyer) dated 07/25/97, acceptability of a qd labeling for the PNAR indication of Flonase, based on clinical trials conducted with a bid dosing regimen (which the sponsor has submitted in this efficacy supplement), will be based on demonstration that the qd administration has clear comparable efficacy to the same total daily dose administered bid and that the sponsor has adequate data to support the efficacy of bid dosing in PNAR. This clinical issue is discussed in further detail in section V. below.

II. Foreign Marketing and Regulatory History:

Flonase aqueous nasal spray [redacted] (50 mcg/actuation) received its first regulatory approval March 8, 1990 in the U.K (for SAR in adults) and has been marketed in the U.K. since 1991.

Flonase aqueous nasal spray [redacted] (50 mcg/actuation) was approved for marketing in adult patients with SAR and PAR in the U.S. on 10/19/94, and an efficacy supplement for the pediatric population (age 4 and above) for SAR and PAR was approved on ____. Flonase has likewise been approved in more than 70 countries throughout the world and the approved indications expanded to include allergic and perennial (allergic and non-allergic) rhinitis in children [Efficacy Supplement for NAPR, NDA 20-121, Vol 36:62-63]. There have been no withdrawals of this product from marketing for any reason related to safety or efficacy. Approved dose regimens for adults and children are generally consistent. The maximum daily dose does not exceed 400 mcg.

III. Preliminary Label Review:

As per the Flonase Aqueous Nasal Spray label, the label for this efficacy supplement will consist of an indication for the treatment of symptoms of seasonal and perennial allergic rhinitis in adults and pediatric patients 4 years of age and older and will additionally include an indication for treatment of non-allergic perennial rhinitis (NAPR) in this same age group. Proposed total nasal symptoms treated effectively with Flonase are to include: rhinorrhea, nasal obstruction. sneezing, and nasal itching and these symptoms for the proposed NAPR indication are the same as those already included in the current Flonase label.

Dosing of Flonase will be either 200 mcg qd (2 sprays in each nostril once a day) or 100 mcg bid (1 spray in each nostril twice a day) for adults, with reduction to 100 mcg qd (1 spray in each nostril) as a maintenance dose, if feasible. The pediatric and adolescent dose of Flonase (age 4-16 years) will be 100 mcg qd (1 spray in each nostril once a day) with an indication in the label to increase the dose to 200 mcg qd if the

patient does not have adequate control of symptoms. Similar to adult patients, the label recommends that once adequate control is achieved, the dose of Flonase be decreased to 100 mcg qd.

Aside from changes in the number of patients studied (which incorporate those patients evaluated in the pivotal Flonase NAPR studies submitted in this efficacy supplement to those evaluated in the original Flonase NDA (#20-121), along with the addition of non-allergic perennial rhinitis indication, and the addition of an adverse event table which includes separate AE frequencies for the 100 mcg and 200 mcg doses of fluticasone; the label for the NAPR Flonase efficacy supplement is essentially the same as that of the Flonase label.

IV. Pharmacokinetic Trials

Pharmacokinetic trials were not required by the Agency for approval of this efficacy supplement and hence not included in this submission. In summary, PK trials will not be reviewed for the medical officer evaluation of the efficacy supplement of Flonase Aqueous Nasal Spray for non-allergic perennial rhinitis in adult and pediatric patients age 4 years and older.

V. Clinical Trials:

The pivotal clinical trials for this efficacy supplement will consist of 3 controlled, U.S. trials for the NAPR indication (FLTA 3010, FLN-351, and FLN-351) that will be bridged in terms of bid dosing to qd dosing to 2 PAR trials (FLN-310, FLN-311) that were previously reviewed in NDA 20-121 and which were used to obtain the PAR indication for Flonase in adults and adolescents. Of note, the primary efficacy variable for the pivotal NAPR studies that will be used for this cross-study comparison (to the 2 PAR studies in the original Flonase NDA) will consist of the mean change from baseline in the patient total nasal symptom scores (comprised of the sum of scores for: rhinorrhea, nasal congestion, and postnasal drip; for a maximum TNSS of 300 based on a visual analog scale from 0-100) and will be compared to the primary efficacy variable for the 2 PAR studies (mean change from baseline in the physician-rated total nasal symptom scores; comprised of the sum of scores for: rhinorrhea, nasal congestion, sneezing, and nasal itching; for a maximum TNSS of 400 based on a visual analog scale from 0-100).

A potential problem exists for direct cross-study comparison between the NAPR and PAR studies, for the primary efficacy variables for these 2 types of studies, while similar, are not identical. Furthermore, 'instantaneous' scoring of symptoms for the NAPR studies was performed for both the a.m. and p.m. separately, while 'instantaneous' a.m. scoring was only performed for the symptom of nasal congestion in the PAR studies. Again, this discrepancy in study design between the NAPR and PAR studies will complicate direct clinical comparability conclusions between these bridging studies, however based on prior nasal steroid applications [redacted] direct comparability between these 2 types of studies will not preclude approval if the proposed Flonase dose **in the NAPR studies** is shown to demonstrate statistically significant efficacy for the primary efficacy variable, as compared to placebo.

Of note, the 'end-of-dosing' interval--felt by the Pulmonary Division to be a important review issue for drug approval, would be affected by the discrepancy in what nasal symptoms are recorded on awakening, again when making direct comparison to the PAR studies; as the PAR studies have a.m. scoring only for the nasal congestion endpoint (the other nasal symptoms are physician-rated at the clinic visit and hence do not represent the 'end-of-dosing' interval). Nonetheless, adequate 'end-of-dosing' information for the 3 NAPR studies are available as total nasal symptoms (along with the individual nasal symptoms) were recorded by patients in their symptom diaries and tabulated by the sponsor. These data will serve as the basis for review of 'end-of-dosing' efficacy for the specific NAPR indication.

While the NAPR studies were not conducted in children, the sponsor has received Pulmonary Division consensus that results could be extrapolated to the pediatric population if an indication for use of Flonase in pediatric patients with SAR/PAR has been approved in the U.S. (which it was).

Non-pivotal trials will consist of controlled non-U.S. studies (6 total) in which PAR and NAPR were not differentiated and 1 uncontrolled non-U.S. trial in which PAR and NAPR were not differentiated.

Finally, 2 controlled studies performed exclusively in pediatric patients age 4-11 years and age 6-11 years, respectively, (non-U.S.) in which PAR and NAPR were not differentiated will also be reviewed.

VI. Safety Concerns:

Aside from the possibility for known potential side effects associated with all intranasal corticosteroids, no particular safety concerns are evident on initial evaluation of this efficacy supplement. There is extensive marketing experience with Flonase nasal spray world-wide. Nonetheless, specific adverse events that will be evaluated closely during this efficacy review will consist of: (1) nasal septal perforations/ulcerations, (2) nasal/oral candidiasis, (3) oral herpes, (4) cataracts, (5) glaucoma, and (6) hyperglycemia.

As part of the NAPR program, effects of Flonase on HPA-axis suppression will be evaluated in studies in all 3 NAPR studies, with pre- and post-treatment Cortrosyn stimulation testing at screening, week 4, and month 6 performed in study FLTA-3010, and a.m. cortisol testing (at screening and week 4 for study FLN-351 and at screening, week 4, and week 6 for study FLN-350) performed in the other 2 NAPR studies. Specific evaluation for increased intraocular pressure or cataract formation was not performed in the NAPR studies. Ophthalmic examinations were performed for the 2 PAR studies used for approval of the PAR indication in NDA 20-121.

VII. Other Relevant Review Issues:

None at this time.

VIII. NDA Completion Timeline:

It is anticipated that complete review (excluding labeling review) of this application, given a generous time-frame, should be accomplished [redacted]. We will be awaiting the sponsor's onset of action data for support of labeling claims, which should become available in February of 1998.

Reviewed by,

[redacted] M.D. 02/04/98

Alexandra S. Worobec, M.D.
Medical Officer, HFD-570

2/5/98

APPEARS THIS WAY
ON ORIGINAL

cc: Division File
cc: Martin H. Himmel, M.D., Deputy Director
cc: John K. Jenkins, M.D., Division Director
cc: David Hilfiker/Project Manager
cc: Cathie Schumaker/Supervisory Project Manager